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L5: Entry 17 of 19 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756120 A
TITLE: Antibiotic formulation and use for drug resistant infections

Brief Summary Text (16):
Since the chemical composition of many drugs precludes their intravenous administration, liposomes can be very useful in adapting these drugs for intravenous delivery. Many hydrophobic drugs, including cyclosporine, fall into this category because they cannot be easily dissolved in a water-based medium and must be dissolved in alcohols or surfactants which have been shown to cause toxic reactions in vivo. Liposomes, composed of lipids, with or without cholesterol, are nontoxic. Furthermore, since liposomes are made up of amphipathic molecules, they can entrap hydrophilic drugs in their interior space and hydrophobic molecules in their lipid bilayer. Although methods for making liposomes are well known in the art, it is not always possible to determine a working formulation without undue experimentation.

Brief Summary Text (20):
Liposomes are provided in the present invention which comprise an aminoglycoside wherein the liposomes are unilamellar having an average size of 100 nm or less. A liposomal formulation is provided which comprises an aminoglycoside wherein the liposomes are comprised of a neutral lipid, a sterol and a negatively charged lipid. Small unilamellar vesicles are also provided wherein the molar amount of negatively charged lipid is less than 20% of total lipid. A preferred formulation is liposomes having an aminoglycoside wherein the liposomes are unilamellar vesicles having an average size of 30 nm to 100 nm and further comprised of a phosphatidylcholine, cholesterol, and a phosphatidylglycerol wherein the molar amount of phosphatidylglycerol is less than 5% and preferably about 3%. The drug to total lipid ratio is between 1:9 and 1:3 with the preferred ratio at about 1:4. A preferred formulation is also provided comprising liposomes including an aminoglycoside wherein the liposomes are unilamellar vesicles having an average size less than 100 nm wherein the lipids comprise hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidylglycerol in a molar ratio of about 2:1:0.1.

Brief Summary Text (22):
The present invention also provides for the treatment of bacterial infections in mammals comprising preparing a liposomal formulation having an aminoglycoside wherein the liposomes are those described above and which are used to treat infections by introducing a therapeutic effective amount of the liposomes into a mammal. Thus, the present invention provides the use of liposomal aminoglycoside formulations to treat bacterial infections. The bacterial infections treated include opportunistic aerobic gram-negative bacilli such as the genera Pseudomonas. Another aspect of the invention includes the use of the liposomal formulations in the treatment of a bacterial infection caused by P. aeruginosa. The method of treating bacterial infections is not limited to gram-negative infections. The liposomal formulations can be used to treat bacterial infections comprising gram-positive bacilli such as the genera Mycobacterium. The invention is particularly useful for treating mycobacterium which causes tuberculosis-like diseases. Numerous bacterium may be treated using the liposomes described above. The bacteria would include: M. tuberculosis, M. leprae, M. Intracellulare, M. smegmads, M. bovis, M.

kansasi, M. avium, M. scrofilcium, or M. africanum. Liposomal formulations of aminoglycoside are also particularly useful in treating MAC.

Brief Summary Text (23):
A particularly useful aspect of the invention is a method of treating a drug resistant bacterial infection in a patient, comprising the delivery to the patient an effective amount of liposomes comprising an encapsulated aminoglycoside wherein the liposomes are comprised of unilamellar vesicles comprised of a neutral lipid, cholesterol and a negatively charged lipid, and having an average size of less than 100 nm. Experiments performed in vitro establish that liposomal amikacin inhibits and kills drug resistant M. tuberculosis. The experiments performed further establish that liposomal amikacin kills M. tuberculosis whereas the free drug, at equivalent dosage concentration, only inhibits the growth of the bacteria. Killing is defined as a reduction in the number of colony forming units of bacteria from a previous time point. Inhibition is defined as an increase in, or the same number of, colony forming units of bacteria from a previous time point but less than the number of colony forming units shown for untreated cultures at the same time points. Thus, the present invention provides for the killing of the bacteria at tolerable non-toxic levels in cases where the bacteria is resistant to aminoglycosides and other antibiotics or where the free drug has at the most an inhibitory effect.

Brief Summary Text (30):
The present invention provides liposomal aminoglycoside formulation preferably containing a neutral lipid such as a phosphatidylcholine, a phosphatidylglycerol, cholesterol (CHOL) and amikacin. Preferred lipid include lipids which are chemically pure and/or are fully saturated. The preferred neutral lipids are saturated lipids such as hydrogenated egg phosphatidylcholine (HEPC), hydrogenated soy phosphatidylcholine (HSPC), distearoyl phosphatidylcholine (DSPC), and dipalmitoyl phosphatidylcholine (DPPC). The preferred carbon chain lengths of the neutral lipids are from C.sub.16 -C.sub.18. The preferred negatively charged lipids are saturated lipids such as hydrogenated soy phosphatdylglycerol (HSPG), hydrogenated egg phosphatidylglycerol (HEPG), distearyolphosphatidylglycerol (DSPG), dimyristoylphosphatidylcholine. Hydrogenated soy phosphatidylcholine (HSPC), distearoylphosphatidylglycerol (DSPG) are the preferred lipids for use in the invention. Other suitable phosphatidylcholines include those obtained from egg or plant sources, or those that are partially or wholly synthetic. Other phosphatidylglycerols that may be used are saturated semisynthic lipids having carbon chain lengths from C.sub.12 -C.sub.18 and include dimyristoyl phosphatidylglycerol (DMPG) and dilaurylphosphatidylglycerol (DLPG).

Brief Summary Text (32):
The process of the present invention is initiated with the preparation of a solution from which the liposomes are formed. A quantity of a phosphatidylcholine, a phosphatidylglycerol and cholesterol is dissolved in an organic solvent, preferably a mixture a 1:1 (by volume) mixture of chloroform and methanol, to form a clear solution. Other solvents (and mixture thereof), such as ether, ethanol and other alcohols can be used. The preferred temperature to dissolve the lipids is between room temperature and 60.degree. C., preferably at room-temperature.. The solution is evaporated to form a lipid film or a lipid powder. To form a lipid film, the solvents are evaporated under nitrogen between room temperature and 60.degree. C., preferably at room temperature. To form a lipid powder, the mixture of lipids in solution as described above is sprayed in a spray drier. Preferably, the spraying takes place under nitrogen.

Brief Summary Text (37):
The above described formulations are also efficacious in inhibiting and killing both drug resistant and drug susceptible M. tuberculosis as established by in vitro testing. In one experiment the drug resistant strain Vertulla of M. tuberculosis was tested. In another experiment the drug susceptible strain H37RV was tested. The

experiments were carried out as described in Example 6. Briefly, human monocytes derived macrophage cultures were developed and infected with either the drug resistant strain or the drug susceptible strain. Liposomal amikacin was prepared as described in Example 1 below. The liposomes comprised HSPC, cholesterol and DMPG in a molar ration of about 2:1:0.1. The drug to total lipid ratio was 1:4 (about 25%). The average size of the liposomes was under 100 nm.

Detailed Description Text (2):
A lipid mixture of hydrogenated soy PC, cholesterol, and distearoyl phosphatidylglycerol was provided in a molar ratio of 2:1:0.1 respectively. The lipids were dissolved in chloroform and methanol (1:1 by volume). The resulting solution was stirred until the lipids dissolved and a clear solution was formed. The mixing is best carried out at room temperature. A lipid film was obtained by evaporating the organic solvents under Nitrogen at room temperature.

CLAIMS:

1. A method of treating a bacterial infection in a patient comprising the delivery to the patient of an effective amount of liposomes consisting essentially of an encapsulated aminoglycoside, wherein the liposomes are comprised of cholesterol, a neutral amphiphilic lipid and a negatively charged amphiphilic lipid, wherein said negatively charged amphiphilic lipid is less than 20% of the total lipid, wherein the aminoglyoside to total lipid molar ratio is from 1:9 to 1:3 and wherein the liposomes consist of unilamellar vesicles having an average size of less than 100 nm.

3. The method of claim 1 wherein the neutral amphiphilic lipid, cholesterol and negatively charged amphiphilic lipid are in a molar ratio of about 2:1:0.1.

28. A method of inhibiting bacterial growth in a patient comprising the delivery to the patient of an effective amount of liposomes consisting essentially of an encapsulated aminoglycoside, wherein the liposomes are comprised of cholesterol, a neutral amphiphilic lipid and a negatively charged amphiphilic lipid, wherein the aminoglycoside to the total lipid molar ratio is from 1:9 to 1:3, wherein the negatively charged amphiphilic lipid is less than 20% of the total lipid and wherein said liposomes consist of unilamellar vesicles having an average size of less than 100 mm.

29. A method of treating a bacterial infection in a patient comprising the delivery to the patient of an effective amount of liposomes consisting essentially of encapsulated amikacin, wherein the liposomes are comprised of cholesterol, HSPC, and DSPG, wherein the amikacin to total lipid molar ratio is from 1:9 to 1:3 and wherein said liposomes consist of unilamellar vesicles having an average size of less than 100 nm.

31. The method of claim 29 wherein HSPC:cholesterol:DSPG are in a molar ratio of about 2:1:0.1.

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L5: Entry 12 of 19 File: USPT Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972379 A
** See image for Certificate of Correction **
TITLE: Liposome composition and method for administering a quinolone

Brief Summary Text (2):
The present invention relates to a composition for administration of a quinolone for treatment of a bacterial infection, and more particularly to a liposome composition for administration of a drug-conjugate of ciprofloxacin covalently attached to an amino acid.

Detailed Description Text (26):
The liposomes may additionally include lipids that can stabilize a vesicle or liposome composed predominantly of phospholipids. The most frequently employed lipid from this group is cholesterol at levels between 25 to 45 mole percent.

Detailed Description Text (27):
Liposomes used in the invention preferably contain between 30-75 percent phospholipids, preferably phosphatidylcholine (PC), 25-45 percent cholesterol, and 1-20 percent polymer-derivatized lipid, expressed on a molar percent basis. One exemplary liposome formulation contains 50 mole percent phosphatidylcholine and 45 mole percent cholesterol and 5 mole percent of a polymer-derivatized lipid, mPEG-DSPE, now to be described.

Detailed Description Text (78):
Liposome having a surface-coating of polyethylene glycol were prepared by dissolving 661.1 mg hydrogenated soy phosphatidylcholine (HSPC), 220.5 mg cholesterol and 220.5 mg of polyethylene glycol derivatized to disteroyl phosphatidylethanolamine (PEG-DSPE) in 10 ml chloroform in a 250 mL round bottom flask. The chloroform was removed using a flash evaporator under reduced pressure until dryness. To the thin lipid film on the surface of the flask was added 15 ml of a solution of 250 mM ammonium sulfate, pH 5.5 and the lipids were dispersed in the solution by vigorous shaking for approximately 30 minutes at 60.degree. C. The multilamellar vesicles obtained were extruded 6 times through a 0.4 .mu.m pore-size Nucleopore polycarbonate filter, 6 times through a 0.1 .mu.m polycarbonate filter and 3 times through a 0.05 .mu.m polycarbonate filter using a stainless steel extrusion cell under a pressure of 200-400 psig. The extrusion process was carried out at 60.degree. C. Liposomes after the extrusion process had a mean-diameter of 100.+-.30 nm. The liposomes were then dialyzed overnight against 4 liters 10% sucrose to remove external ammonium sulfate at 4.degree. C.

Detailed Description Text (91):
Liposomes were prepared as described above in Comparative Example 1 by dissolving 585 mg hydrogenated soy phosphatidylcholine (HSPC), 261 mg cholesterol and 210 mg of PEG-DSPE (prepared as described, for example, in Zalipsky (1995) to form liposomes with the following composition: 50% HSPC, 45% cholesterol and 5% mPEG-DSPE.